Disorders of the Motor Unit

MHD Clinical Correlation– Neuroscience Block

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Motor neuron disease (MND)

MNDs are classified according to whether they are inherited or sporadic, and to whether degeneration affects upper motor neurons, lower motor neurons, or both

• Spinal muscular atrophies
  – Hereditary diseases affecting the lower motor neurons
  – Autosomal recessive caused by defects in the gene SNR1 (survival of motor neuron protein)
  – LMN signs of weakness, atrophy, areflexia, fasciculations

• Amyotrophic Lateral Sclerosis (ALS)
  – Heterogeneous, many different genes and pathological processes
  – Progressive loss of motor neurons in the brain and spinal cord
  – More common in men, peak onset 50-70 years of age, survival variable, death usually in 3-4 yrs.
  – Clinical presentations
    • Typical ALS: 70%; UMN+LMN, bulbar or spinal
    • ALS + Frontotemporal degeneration (FTD; behavioral variant): 5-15%
    • Other variants: isolated bulbar, “isolated” LMN, “isolated” UMN

Amyotrophic lateral sclerosis

• Frequently begins with regional weakness and atrophy of a limb (e.g., shoulder), which spreads and becomes bilateral, or initial weakness of swallowing or speech
• Diffuse fasciculations may be prominent
• Hyporeflexia, spasticity and Babinski signs
• Weakness eventually affects speech, chewing, swallowing, and breathing

• Diagnosis
  – No test to definitively diagnose (clinical picture, EDX and r/o mimics)

• Treatments
  – Symptomatic; nutritional, respiratory, physical therapy
  – Riluzole® (glutamate antagonist) prolongs survival by months
  – Edaravone® (a free radical scavenger) slows functional decline
## Neuropathies - Mononeuropathy

**MONONEUROPATHY**
- A single, major nerve is involved, with sensory or motor deficits related to its anatomical distribution;
- Diagnosis is often made from clinical findings; EDX can help localize and assess severity of the nerve lesion;
- Usually caused by trauma or compression;
- Focal demyelination of a nerve may occur where the nerve tends to be compressed, accompanied by axonal damage if a severe lesion

### Median mononeuropathy at the wrist (carpal tunnel syndrome)
- Most common mononeuropathy (others include ulnar mononeuropathy from leaning or falling on the elbow or peroneal mononeuropathy from an injury to the lateral knee)
- Compression of the median nerve as it passes through the carpal tunnel
- Tingling numbness of the hand may awaken the patient, while thenar weakness and atrophy occur in more severe cases
- Treatment of compressive mononeuropathies include local rest, anti-inflammatory medication, splinting, to surgical decompression of the nerve

## Neuropathies - Polyneuropathy

**POLYNEUROPATHY (OR PERIPHERAL NEUROPATHY)**
- A disorder of multiple, major and small nerves
- Early sensory loss or impairment in distal limbs (feet, with longest sensory fibers in body, then hands - "stocking & glove"
- Spontaneous tingling, "pins & needles" (anesthesia) and unpleasant sensation from non-noxious stimulus (dysesthesia)
- Distal limb weakness and atrophy
- Early loss or decrease of muscle stretch reflexes

## Polyneuropathy Classification

- Symmetric proximal and distal weakness minimal sensory loss (e.g., Guillain-Barré syndrome)
- Symmetric distal weakness with sensory loss (e.g., diabetes, alcohol, cryptogenic, hereditary)
- Asymmetric distal weakness and sensory loss (e.g., Vasculitis, Infectious)
- Asymmetric distal weakness without sensory loss (e.g., motor neuron disease)
- Asymmetric proximal and distal weakness with sensory loss (e.g., diabetes, infiltrative, toxins)
- Symmetric sensory loss without weakness (e.g., metabolic, toxins, idiopathic)
- Asymmetric proprioceptive sensory loss with weakness (e.g., paraneoplastic, HIV, B6 toxicity)
- Autonomic symptoms and signs (e.g., Diabetes, amyloidosis)
Pathology of polyneuropathy

- Suggested by EDX testing, or by nerve biopsy
- Demyelination
  - Found in some hereditary neuropathies, or in autoimmune mediated polyneuropathies like Guillain-Barré syndrome, where abnormalities are often asymmetrical or non-uniform
  - If severe, can lead to secondary axonal loss
- Axonal degeneration
  - Is the primary process in most polyneuropathies, possibly from inadequate axoplasmic flow in various metabolic conditions
  - Demyelination may secondarily occur

Evaluation & Treatment of polyneuropathy

- Review patient’s history
  - Hereditary neuropathy suggested by same symptoms in family
  - Toxic neuropathy may be related to certain occupations, hobbies, or medications
- Clues from clinical pattern of nerve involvement
  - Multiple mononeuropathies (SLE, diabetes, others)
  - Autonomic nerve involvement (diabetes, others)
- Blood tests for potential, especially treatable, causes
- Neurophysiological testing (EDX); a test of nerve and muscle function
- (Nerve biopsy in selected cases)
- Treatment
  - Treatment of its primary, underlying cause (e.g., control of diabetes, abstinence from alcohol);
  - Orthotic devices/ Physical therapy
  - Medications to relieve painful sensory disturbances (topical creams or ointments, oral anticonvulsants or antidepressants)

Guillain-Barré Syndrome

- A very acute polyneuropathy, weakness progressing over hours to days, at its worst by 4 weeks
- An ascending (legs first), areflexic paralysis
  - generalized (including respiratory) paralysis may occur
  - some paresthesia, little objective sensory loss
- Occurs at any age
- Patients often have a recent viral respiratory or bacterial infection
- Misdirection of the immune system [gangliosides (GM1, GD1a, GQ1b) are targeted by immunoglobulins and share antigenic epitopes with some bacterial and viral antigens]
**Guillain-Barré Syndrome**

- Pathologically, inflammation and demyelination of peripheral nerves or roots (if severe, secondary axonal loss)
- Diagnosis:
  - evidence of demyelination by EDX testing of nerves
  - elevated protein in CSF, with few if any WBCs
  - serum studies (serology for Campylobacter jejuni; acute and convalescent serology for cytomegalovirus, Epstein-Barr virus, and Mycoplasma pneumoniae)
- Prognosis is overall good with optimal medical care (10% have a disability)
- **Plasmapheresis or immunoglobulin infusions (IVIG)** may shorten the illness and hasten recovery

**Hereditary neuropathies**

- Complex set of disorders caused by mutations in multiple genes
- Involve molecular pathways that cause demyelination, axonal loss or abnormal interactions between Schwann cells and axons
- Onset usually by childhood, but may be subtle
- Distal sensorimotor deficits, little to no paresthesia or dysesthesia
- Typical **orthopedic deformities** present (scoliosis, hammertoes, pes cavus) since neuropathy began in a growing child
- No curative treatment available
- Give assistive devices or orthotics as needed

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**GBS - Pathophysiology**

- C. jejuni
- Cytomegalovirus
- Epstein-Barr virus
- Influenza A
- Mycoplasma pneumoniae
- Haemophilus influenzae
- Hepatitis (A, B, and E)
- Zika virus
Hereditary neuropathies - Classification

- Hereditary Motor and Sensory Neuropathies (HMSN) or Charcot-Marie-Tooth disease (CMT)
  - CMT1 - AD and predominantly demyelinating; Variable genes 50-80% of cases
  - CMT2 - AD and predominantly axonal; Variable genes 10-15% of cases
  - (CMT3) - Dejerine-Sottas disease – severely affected children regardless of inheritance
  - CMT4 – AR
  - CMTX – X-linked inheritance

- Hereditary Sensory and Autonomic Neuropathies (HSAN)
  - HSAN I – AD; Most common form, genetically heterogenous
  - HSAN II – AR; Early onset
  - HSAN III – AR; (Familial dysautonomia, also known as Riley-Day syndrome)
  - HSAN IV – AR; (Congenital insensitivity to pain with anhidrosis), by age 3, 20% die from hyperpyrexia
  - HSAN V – AR; (Congenital insensitivity to pain with anhidrosis and developmental delay)

- Polynuropathies associated with other genetic disorders
  - Systemic manifestations or associated CNS or UMN findings suggest these disorders

Neuromuscular Junction

- Action potential reaches the motor nerve terminal and triggers release of stored calcium into the axoplasm
- Calcium influx facilitates fusion of vesicles, contains Acetylcholine (ACh), to the terminal nerve membrane and releases ACh into the synaptic cleft
- ACh binds to nicotinic acetylcholine receptors (AChR) on the postsynaptic, sarcolemma membrane causing end plate depolarization (EPP)
- If enough ACh is bound, EPP's summate and lead to the activation of a propagating muscle membrane depolarization.
- This depolarization enters the muscle fiber, via T tubules, that trigger release of stored calcium from the sarcoplasmic reticulum
- The sarcoplasmic reticulum release calcium, triggering the interaction of actin and myosin proteins and the visible contraction
- Acetylcholinesterase (AChE) on the postsynaptic (muscle) membrane breaks down ACh, limiting its action, breakdown products are taken up by the nerve terminal and used again
- Normally there is more than enough ACh released with each nerve action potential to ensure summated EPPs initiate a muscle membrane depolarization ("safety factor")

NMJ Disorders

- Postsynaptic: Myasthenia Gravis (MG)
  - Immune target is AChR
- Presynaptic: Lambert-Eaton Myasthenic Syndrome (LEMS)
  - Immune target is the pre-synaptic voltage-gated Ca channel
- Presynaptic: Botulism
  - Exotoxin inhibits ACh release
- Congenital Myasthenia syndromes
  - Genetic disorders disrupting normal NMJ function
  - Abnormal proteins can reside in the nerve terminal, synaptic basal lamina or postsynaptic site
Myasthenia Gravis (MG)

- Begins at any age
- **Ocular MG (10-20%)**
  - Ptosis, diplopia are the only symptoms after 2-3 years
- **Generalized MG (80-90%)**
  - Ptosis, diplopia, dysarthria, dysphagia; respiratory, facial, neck and limb weakness
- Symptom severity varies from patient to patient, remission may occur
- Fatigability occurs with certain activities
- Preserved sensation and reflexes

Neuromuscular junction in Myasthenia Gravis (MG)

- Antibodies to AChR complex (from B-cells helped by T-cells) block receptors and increase degradation and turnover
- Loss of functional AChR leads to weakness
- Normally, after each nerve action potential there is a slight decrease in the readily available ACh to be released, but more than enough (“Safety factor”)
- Normally there is more than enough ACh released to bind with enough AChRs, generate enough EPPs to summate and initiate muscle membrane depolarization, before the AChE degrades the ACh
- Myasthenic fatigue occurs when this normally mild reduction of ACh, released after repetitive nerve action potentials, fails to “find” and interact with enough AChRs to initiate a critical number of EPPs that on summation result in a self-propagating muscle membrane potential

Diagnosis of Myasthenia Gravis (MG)

- Typical clinical features
- **Positive Tension (edrophonium) test**
  - IV injection of short-acting AChE inhibitor
  - EDX evidence of abnormal NMJ transmission
  - Repetitive nerve stimulation – shows a decremental response
- **Elevated serum antibody titer to AChR**
  - High specificity (99%)
  - Present in 80-90% generalized, 50% ocular MG
  - MuSK antibodies found in 40% of generalized MG with absent AChR antibodies
Treatment of Myasthenia Gravis (MG)

- **Anticholinesterase drugs**
  - Pyridostigmine; inhibits AChE, enhancing effect of released ACh
  - Improve symptoms, not autoimmune pathology

- **Thymectomy**
  - Contains AChR-like material, where autoimmune response initiated?
  - Hyperplastic thymus or thymoma (rarer) occur in MG

- **Immunosuppressant drugs**
  - Corticosteroids
  - Azathioprine, Mycophenolate mofetil, Rituximab
  - Acute/transient treatment
    - Plasmapheresis
    - Immunoglobulin infusions

Lambert-Eaton Myasthenic Syndrome (LEMS)

- **Clinical**
  - Fatigable weakness of lower extremities - mimics a myopathy
  - Exertion briefly improves power and hyporeflexia

- **Autoimmune “attack” against presynaptic calcium channels (VGCC)**
  - 50-60% related to small cell lung cancer (paraneoplastic)
  - 40-50% related to a primary autoimmune disorder

- **Diagnosis**
  - Repetitive nerve stimulation tests (Incremental response after voluntary contraction)
  - VGCC antibodies

- **Treatment**
  - 3,4-diaminopyridine (blocks voltage gated potassium channels, prolongs nerve terminal depolarization and increases ACh release)
  - In autoimmune disorders – immunosuppressants similar to those for MG

Myopathy

- **Primary disease of muscle**
  - Hereditary
    - Muscular dystrophies, Channelopathies, Metabolic myopathies, Mitochondrial Myopathies
  - Acquired
    - Inflammatory, Endocrine, Drug-induced, Toxic, Associated with systemic disease

- **Usually proximal limb weakness and atrophy (shoulders, hips)**

- **Late loss of reflexes (after significant atrophy present)**

- **Intact sensation**

- **Diagnosis:**
  - Review of family history (muscular dystrophy)
  - Serum muscle enzymes (CK) are often elevated
  - EDX demonstrates a disorder of muscle
  - Muscle biopsy
Muscular dystrophy

- Hereditary myopathies of variable progression and severity
  (Actually refers to more than 50 distinct diseases defined by specific genetic mutations. Thus, this term is rapidly becoming an anachronism that is likely to be replaced by specific molecular diagnoses)
  - Duchenne muscular dystrophy (DMD)/Becker muscular dystrophy
  - Limb-girdle muscular dystrophy
  - Dilated myopathies
  - Congenital muscular dystrophy
  - Facioscapulohumeral muscular dystrophy
  - Myotonic dystrophy

- Duchenne’s Muscular Dystrophy (X-linked)
  - Virtual absence of dystrophin, critical structural protein, in muscle; also involves respiratory and cardiac muscles
  - Proximal weakness begins in boys of childhood age
  - Calf pseudohypertrophy from muscle replaced by fat, connective tissue
  - Cardiorespiratory death by third decade

Polymyositis

- Inflammation and weakness of muscles (multiple etiologies)

- An immune mediated cause is most common in the USA
  - Proximal weakness over weeks to months
  - If there is an associated rash (often around the eyes or fingers) = Dermatomyositis (DM)
  - Association between inflammatory myopathy (DM > PM) and malignancy in adults
  - PM is estimated between 7% and 30%

- Diagnosis is confirmed by EDX testing, and presence of inflammation and muscle fiber necrosis on biopsy

- Treatment includes corticosteroids or other immunosuppressive drugs